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Verapamil Versus Digoxin and Acute Versus Routine Serial Cardioversion for the Improvement of Rhythm Control for Persistent Atrial Fibrillation

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OBJECTIVES The VERDICT (Verapamil Versus Digoxin and Acute Versus Routine Serial Cardioversion Trial) is a prospective, randomized study to investigate whether: 1) acutely repeated serial electrical cardioversions (ECVs) after a relapse of atrial fibrillation (AF); and 2) prevention of intracellular calcium overload by verapamil, decrease intractability of AF.

BACKGROUND Rhythm control is desirable in patients suffering from symptomatic AF.

METHODS A total of 144 patients with persistent AF were included. Seventy-four (51%) patients were randomized to the *acute* (within 24 h) and 70 (49%) patients to the *routine* serial ECVs, and 74 (51%) patients to verapamil and 70 (49%) patients to digoxin for rate control before ECV and continued during follow-up (2 × 2 factorial design). Class III antiarrhythmic drugs were used after a relapse of AF. Follow-up was 18 months.

RESULTS At baseline, there were no significant differences between the groups, except for beta-blocker use in the verapamil versus digoxin group (38% vs. 60%, respectively, p = 0.01). At follow-up, no difference in the occurrence of permanent AF between the acute and the routine cardioversion groups was observed (32% [95% confidence intervals (CI)] 22 to 44) vs. 31% [95% CI 21 to 44], respectively, p = NS), and also no difference between the verapamil- and the digoxin-randomized patients (28% [95% CI 19 to 40] vs. 36% [95% CI 25 to 48] respectively, p = NS). Multivariate Cox regression analysis revealed that lone digoxin use was the only significant predictor of failure of rhythm control treatment (hazard ratio 2.2 [95% CI 1.1 to 4.4], p = 0.02).

CONCLUSIONS An acute serial cardioversion strategy does not improve long-term rhythm control in comparison with a routine serial cardioversion strategy. Furthermore, verapamil has no beneficial effect in a serial cardioversion strategy. (J Am Coll Cardiol 2006;48:1001–9)

Currently, rate control is the recommended treatment for the majority of patients with atrial fibrillation (AF), provided they are not symptomatic (1,2). However, the randomized rate versus rhythm control studies did not deal with patients highly symptomatic with the arrhythmia (1,2). In these patients, rhythm control with cardioversion and antiarrhythmic drugs or non-pharmacological interventions is desirable (3,4). Still, long-term maintenance of sinus rhythm (SR) is cumbersome. This is mainly caused by atrial electrical and structural remodeling (5–7). Maintenance of SR is associated with reversal of remodeling (8–12). The AF-induced electrical remodeling takes only half a day, and it is considered reversible within 2 to 5 days (9–12). Therefore, in patients undergoing cardioversion for persistent AF, maintaining SR for at least a few days is needed to develop reversed remodeling. In addition, an eventual relapse of AF must be stopped within hours to avoid recurrence of electrical remodeling (12,13).

Atrial calcium overload and reduction of L-type calcium channels are the primary cause of electrical and contractile remodeling (6,7,14). Prevention of intracellular calcium overload by calcium antagonists may decrease intractability of AF by preventing these remodeling processes. In a serial cardioversion strategy, remodeling may happen again and again, and in this setting verapamil has not been tested before.

The development of a safe and effective pharmacological rhythm-control strategy would have a major impact on the treatment of AF. Considering the above, we hypothesized that an acute serial cardioversion strategy, by enhancing and consolidating reversed remodeling, could improve arrhythmia outcome in persistent AF. In addition, we reasoned that in this setting verapamil, by preventing repeated intracellular calcium overload, may enhance reversed remodeling and help to slow recurrent remodeling with each recurrence. Therefore, we

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Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
ECV = electrical cardioversion
INR = international normalized ratio
IRAF = immediate reinitiation of atrial fibrillation
LV = left ventricle/ventricular
NYHA = New York Heart Association
SR = sinus rhythm

investigated whether during a serial electrical cardioversion (ECV) strategy, 1) acute cardioversion of subacute recurrences, and 2) prevention of intracellular calcium overload by verapamil in case relapses occur, will decrease intractability of persistent AF. In addition, the influence of the acute strategy on quality of life was investigated.

METHODS

Study design. Seven centers in the Netherlands participated in the study (Appendix). All patients gave written informed consent. The institutional review boards of all hospitals approved the study protocol. The study started in June 2001. Total follow-up was 18 months in all patients.

Only patients with persistent AF without contraindication for oral anticoagulation were included. Persistent AF was defined as non–self-terminating arrhythmia and requiring ECV to obtain SR (15). Patients were excluded if the current episode of AF had lasted longer than 1 year or if any previous ECV was unsuccessful. A maximum of 1 previous ECV during the last year was allowed. Patients were also excluded if they had unstable angina pectoris, a recent myocardial infarction or cardiac surgery (<4 weeks), current infection or thyroid disturbances, atrial flutter, a concurrent untreated medical condition, were unlikely to comply with the protocol, heart failure New York Heart Association (NYHA) functional class III or IV, current or previous treatment with amiodarone, or a pacemaker.

This was a randomized open study. Patients were randomized to: 1) *acute* (using transtelephonic monitoring to identify relapses of AF twice a day and guarantee acute ECVs within 24 h) or *routine* (rhythm follow-up at the outpatient clinic) serial ECVs; and 2) *verapamil* (120 to 360 mg daily) or *digoxin* (0.125 to 0.25 mg daily, after loading, depending on age, heart rate, and renal function) for rate control before ECV and continued during total follow-up (2×2 factorial design) (Fig. 1). The target was a resting heart rate <100 beats/min (monitored with a 12-lead resting electrocardiogram) (2). If patients were treated with verapamil or digoxin before inclusion, the drugs were discontinued after randomization, and patients received verapamil or digoxin according to the randomization. If patients were using a beta-blocker, they were allowed to continue this drug.

From 4 weeks before until 4 weeks after ECV, all patients received phenprocoumon or acenocoumarol (target international normalized ratio [INR] 2.5 to 3.5, according to the Netherlands guidelines). Anticoagulation was monitored at a regional center of The Netherlands Thrombosis Services, which specializes in monitoring anticoagulant treatment in outpatients. If SR was present at 1 month, the oral anticoagulant could be stopped or changed to aspirin (80 to 100 mg daily), depending on stroke risk factors. Two weeks after randomization, the patients visited the outpatient clinic for physical examination, transthoracic echocardiography, and a 24-h Holter monitor to assess rate control. The ECV was scheduled 1 month after randomization and was performed only if anticoagulant treatment had been adequate. After this first ECV, patients followed their randomized ECV strategy, including those who had spontaneous conversion to SR before the first ECV. All patients continued verapamil or digoxin throughout the study.

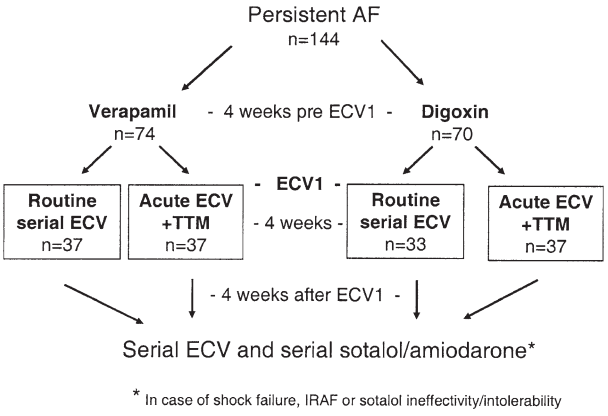

Figure 1. Study flow chart. AAD = antiarrhythmic drug; AF = atrial fibrillation; ECV = electrical cardioversion; IRAF= immediate reinitiation of AF; TTM = transtelephonic monitoring.

Electrical cardioversion was performed during light general anesthesia by using 20 mg of etomidate intravenously. A calibrated mono- or biphasic defibrillator, which could store 360 or 200 J of energy, respectively, was used as a cardioversion device. We started with 100 or 50 J of stored energy, respectively. Thereafter, energy load of successive shocks was doubled until SR was restored or after 2 attempts at the highest level. All shocks were applied to the chest in an anterior-lateral paddle configuration. Immediate outcome of the shock was monitored by continuous 12-lead electrocardiogram for 5 min. Post-shock rhythm monitoring was secured by telemetry for 4 h.

Patients visited the outpatient department 1, 3, 6, 12, 15, and 18 months after cardioversion. At each visit, complaints, cardiovascular events, physical examination, and a 12-lead electrocardiogram were recorded. Additional visits were performed 1 month after each re-ECV. During the first month, patients randomized to the acute group monitored and transmitted their heart rhythm twice a day to the Holter analysis department of the University Medical Center Groningen by using a wrist-electrocardiogram recorder. Two experienced Holter technicians judged all wrist-electrocardiograms. After this month, patients received

instructions concerning recurrence detection, and in case of a relapse, they were instructed to come to the hospital immediately in order to perform ECV within 24 h. After each recurrence after the first month, they used the wrist-electrocardiogram recorder twice a day for another 2 weeks.

If in the acute cardioversion group the first study ECV was unsuccessful, amiodarone was instituted according to the schedule mentioned in the following text. In case of a relapse, ECV was repeated as soon as possible, but always within 24 h after relapse of AF. The first month after the first cardioversion, no antiarrhythmic drugs were instituted (except for amiodarone for 2 weeks; see the text that follows), regardless of the number of preceding ECVs. In the case of an unsuccessful re-ECV (i.e., no SR restored during ECV, or untreatable immediate reinitiation of atrial fibrillation [IRAF], or a relapse of AF within 4 h after ECV), patients received amiodarone: immediately after unsuccessful (repeat) ECV, 300 mg amiodarone intravenously in 30 min, followed by 1,200 mg during the next 24 h. Repeat ECV was performed 24 h after loading with amiodarone. In the case of chemical conversion or successful repeat ECV, amiodarone was continued orally at 600 mg daily for 2 weeks. Amiodarone was used as the first-choice drug because we expected that this drug would most effectively prevent recurrences. Amiodarone was used as a temporary drug; i.e., after maintaining SR for at least 2 weeks, the drug was stopped. In the case of an unsuccessful repeat ECV, amiodarone orally (600 mg daily) was continued for 4 weeks. Subsequently, in the case of no chemical conversion, ECV was repeated (see routine cardioversion group). In the case of a relapse after 1 month, prophylactic antiarrhythmic drugs were instituted (see routine cardioversion group), but the *acute strategy still applied.* If the combination of a class III antiarrhythmic drug with verapamil or digoxin led to symptomatic sinus bradycardia, AV conduction disturbances, or low blood pressure, dosages of verapamil or digoxin were lowered or discontinued.

In the routine cardioversion group, after the first cardioversion, no antiarrhythmic drugs were instituted. After a relapse, patients started with sotalol (240 to 320 mg daily) and, in the case of another relapse within 3 months, amiodarone (600 mg daily for 4 weeks before ECV, followed by 200 mg daily after ECV) was instituted. Relapses, which occurred ≤3 months of SR, were interpreted as failure of the antiarrhythmic drug presently instituted, and these patients continued to the next drug. Sotalol, but not amiodarone, was instituted in-hospital during 24 h of telemetric monitoring. We did use sotalol and not amiodarone as a first-line treatment in case of a recurrence to comply as much as possible with the routines in our clinic. Obviously, amiodarone would have prevented recurrences better than sotalol or flecainide, but it was not used to avoid as much as possible its potential side effects (3). In the case of a relapse of AF, a repeat ECV was scheduled as hospital routines dictated, but always within 4 to 6 weeks.

The primary end point was permanent AF, which was defined as acceptance of AF if patients experienced a relapse of AF within 3 months after cardioversion or shock failure while on amiodarone, provided adequate plasma levels (amiodarone and desethylamiodarone cumulative plasma levels >2.0 mg/l), or if patients had a relapse of AF and antiarrhythmic drug-related side effects, or if patients refused another ECV.

Quality of life. Quality of life was assessed using the Medical Outcomes Study Short-Form health survey (SF-36) questionnaire. The SF-36 is a standardized, validated, generic health survey that has been frequently used in arrhythmia studies. The SF-36 has been translated and validated in the Netherlands (16). Quality of life was determined at baseline and at the end of follow-up.

Statistical analysis. The primary objective was to test our hypothesis that acute cardioversion after a relapse of AF will decrease intractability of AF, i.e., permanent AF. This study was originally powered to detect a relative difference of 50% in permanent AF, which was based on our results from a previous cardioversion study (17). With 40% permanent AF in the acute cardioversion group versus 60% in the routine cardioversion group after 18 months of follow-up, 240 patients were needed to reach statistical significance with a power of 80% and alpha of 0.05 (two-sided). The present manuscript describes the final results of the VERDICT (Verapamil Versus Digoxin and Acute Versus Routine Serial Cardioversion Trial) after 144 patients had completed the study, at the time of the planned interim analysis. With 32% versus 31% permanent AF in the acute versus the routine cardioversion group, it was decided to stop further inclusion of patients. A secondary aim of this study was to investigate whether prevention of intracellular calcium overload by verapamil (but not by digoxin) will reduce permanent AF. The baseline characteristics of patients were compared with chi-square tests and *t* tests. For all time-to-event analyses, Kaplan-Meier estimates were used and were compared by the log-rank test. Univariate and multivariate Cox regression analyses were performed to determine predictors of permanent AF. For categorization of continuous variables, cutoff points were chosen on the basis of clinical relevance or the median value. The univariately analyzed variables included gender, age, hypertension, coronary artery disease, valvular heart disease, diabetes, heart failure, cardiomyopathy, respiratory disease, AF duration, previous ECV(s), previous antiarrhythmic drug use, body mass index, blood pressure, heart rate, echocardiographic atrial and ventricular dimensions, medication use (including verapamil and digoxin use), and ECV strategy (acute versus routine). All univariate variables with $p < 0.10$ were added to the multivariate model. In multivariate models, interaction was investigated. All tests performed in order to test the (null-) hypothesis of no treatment difference were two-sided. Patient data were used in accordance with the intention-to-treat principle. A $p < 0.05$ was considered statistically significant. For all analyses, commercially available com-

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puter software (Statistical Analysis System version 6.12, SAS Institute, Cary, North Carolina) was used.

RESULTS

Characteristics of the patients. A total of 144 patients were enrolled in the study. At inclusion (1 month before ECV), 74 (51%) were randomized to the acute and 70 (49%) to the routine cardioversion group. Furthermore, 74 (51%) patients were randomized to verapamil and 70 (49%) to digoxin for rate control (Fig. 1).

Acute versus routine serial cardioversion. There were no significant differences in baseline characteristics (Table 1). In the acute and routine groups, 43 (58%) and 39 (56%) patients, respectively, had an unsuccessful ECV or a subacute recurrence of AF ≤30 days (p = NS) (Fig. 2). Late recurrences >30 days after the first study ECV occurred in 20 (27%) and 17 (24%) of the acute and routine randomized patients, respectively (p = NS). Nine (12%) and 10 (14%) patients maintained SR during the total follow-up, respectively (p = NS). After 18 months, no difference in permanent AF between both groups was

Table 1. Baseline Characteristics of Patients Randomized to the Acute Versus Routine Serial Cardioversion Group and Randomized to Digoxin Versus Verapamil

	Acute (n = 74)	Routine (n = 70)	Digoxin (n = 70)	Verapamil (n = 74)
Age, yrs	65 ± 11	66 ± 8	65 ± 11	65 ± 8
Male gender, no. (% of patients)	46 (62)	43 (61)	46 (66)	43 (58)
Total history of AF, days	138 (47–730)	113 (43–285)	140 (51–716)	117 (42–304)
Duration of current episode of AF, days	60 (27–138)	61 (33–125)	56 (32–124)	70 (30–138)
Previous ECV(s), no. (% of patients)				
0	60 (81)	58 (83)	54 (77)	64 (87)
1	10 (14)	11 (16)	13 (19)	8 (11)
2	4 (5)	1 (1)	3 (4)	2 (3)
Sinus rhythm duration after last ECV, months	13 (3–42)	11 (1–53)	15 (3–47)	6 (1–46)
Coronary artery disease, no. (% of patients)	11 (15)	11 (16)	13 (19)	9 (12)
Old myocardial infarction, no. (% of patients)	7 (9)	7 (10)	8 (11)	6 (8)
Valve disease, no. (% of patients)				
Aortic	0 (0)	4 (6)	2 (3)	2 (3)
Mitral	12 (16)	8 (11)	9 (13)	11 (15)
Aortic and mitral	1 (1)	2 (3)	0 (0)	3 (4)
Cardiomyopathy, no. (% of patients)	3 (4)	3 (4)	2 (3)	4 (5)
Dilated	3 (4)	2 (3)	2 (3)	2 (3)
Hypertrophic	0 (0)	1 (1)	0 (0)	2 (2)
History of hypertension, no. (% of patients)	37 (50)	30 (43)	29 (41)	38 (51)
History of chronic obstructive lung disease, no. (% of patients)	12 (16)	4 (6)	7 (10)	9 (12)
History of diabetes mellitus, no. (% of patients)	5 (7)	8 (11)	5 (7)	8 (11)
No apparent heart disease, no. (% of patients)	26 (35)	26 (37)	25 (36)	27 (36)
Heart failure, no. (% of patients)				
NYHA functional class I	69 (93)	66 (94)	65 (93)	70 (95)
NYHA functional class II	5 (7)	4 (6)	5 (7)	4 (5)
Complaints, no. (% of patients)	59 (80)	58 (83)	56 (80)	61 (82)
Dyspnea	43 (58)	36 (51)	37 (53)	42 (57)
Fatigue	30 (41)	36 (51)	27 (39)	39 (53)
Palpitations	26 (35)	18 (26)	23 (33)	21 (28)
Previous class I and III AADs, no. (% of patients)	10 (14)	11 (16)	10 (14)	11 (15)
Medication use, no. (% of patients)				
ACE inhibitor or ARB	36 (49)	25 (36)	25 (36)	36 (49)
Diuretics	25 (34)	27 (39)	27 (39)	25 (34)
Lipid-lowering drugs	10 (14)	10 (16)	12 (17)	9 (12)
Acenocoumarol or phenprocoumon	74 (100)	70 (100)	70 (100)	74 (100)
Blood pressure, mm Hg				
Systolic	141 ± 20	142 ± 21	140 ± 19	143 ± 22
Diastolic	86 ± 10	87 ± 15	85 ± 10	88 ± 15
Body mass index	29 ± 5	29 ± 6	29 ± 5	29 ± 6
Echocardiographic findings, mm				
Size of left atrium long axis	45 ± 7	46 ± 6	45 ± 6	46 ± 6
Left ventricular end-diastolic diameter	51 ± 6	52 ± 6	52 ± 6	51 ± 6
Left ventricular end-systolic diameter	36 ± 8	36 ± 8	37 ± 8	35 ± 7
Septal thickness	11 ± 2	11 ± 3	11 ± 3	10 ± 2
Posterior-wall thickness	10 ± 1	10 ± 2	10 ± 2	10 ± 2
Fractional shortening	31 ± 9	31 ± 9	30 ± 10	32 ± 8

AAD = antiarrhythmic drug; ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ECV = electrical cardioversion; NYHA = New York Heart Association.

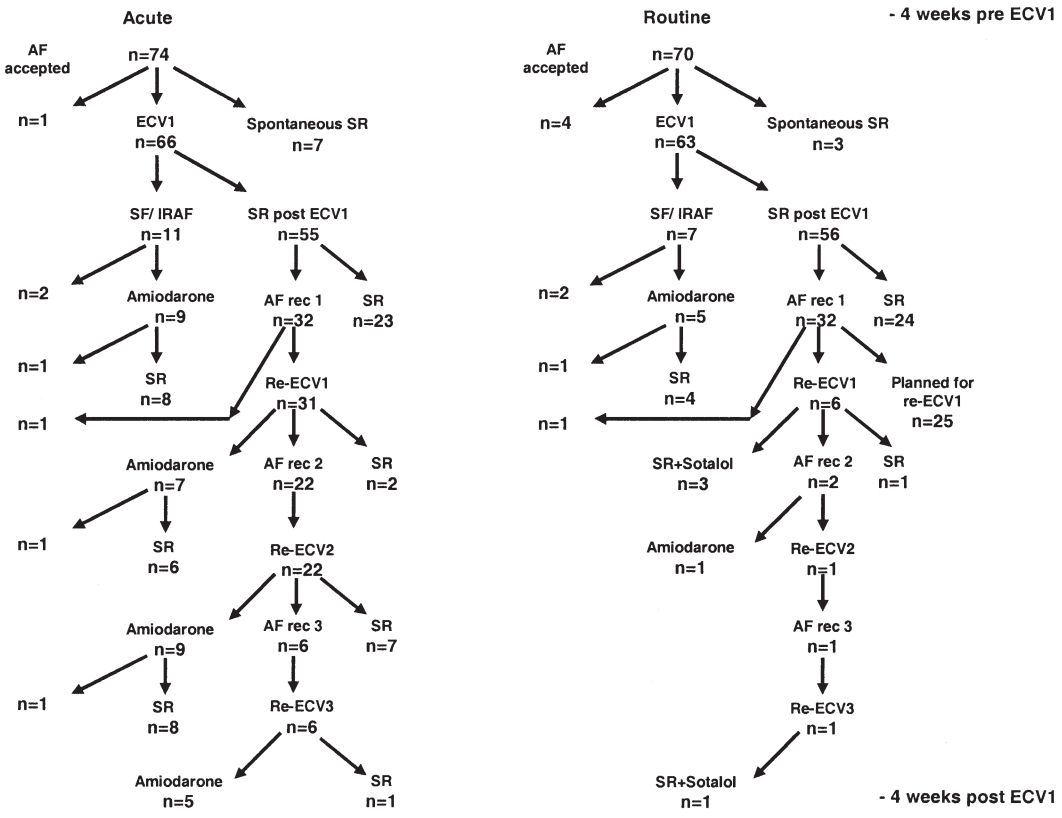

Figure 2. Recurrence pattern and treatment of recurrent atrial fibrillation during the first 4 weeks in the acute versus routine group. SF = shock failure; SR = sinus rhythm; other abbreviations as in Figure 1.

observed (32% [95% confidence interval (CI) 22 to 44] [n = 24] vs. 31% [95% CI 21 to 44] [n = 22], p = 0.85) (Fig. 3), despite more ECVs in the acute versus the routine group (median 3 vs. 2, $p < 0.05$, and ≥3 ECVs in 54% vs. 33%, respectively; $p < 0.01$).

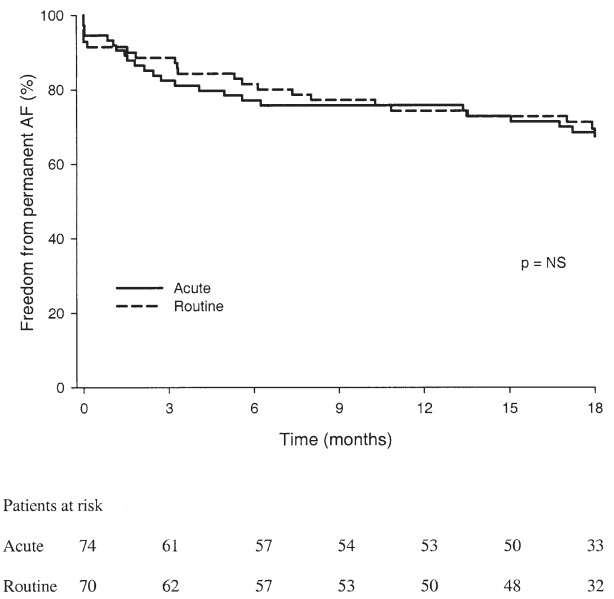

Figure 3. Freedom from permanent atrial fibrillation in acutely versus routinely treated patients. Abbreviations as in Figure 1.

No significant differences in medication use between both groups at ECV, and after 1 and 18 months of follow-up were present, except for amiodarone use after 1 month (40% vs. 9% of patients in the acute versus the routine cardioversion group, respectively; $p < 0.001$) and sotalol use at 18 months (4% vs. 23%, respectively; $p < 0.05$) (Table 2). Amiodarone was started in 16 patients because of shock failure (12 vs. 4 patients in the acute vs. the routine group, respectively; $p < 0.05$), in 21 patients because of IRAF (15 vs. 6 patients in the acute versus the routine group, respectively; $p < 0.05$), and in 36 patients because of repeated

Table 2. Medication During the Study of Patients Randomized to the Acute Versus Routine Serial Cardioversion Group

Drug	Strategy	At ECV1*	1 Month After ECV1*	Permanent AF/EoS*
Digoxin	Acute	37 (50)	37 (50)	27 (37)
	Routine	33 (47)	33 (47)	30 (43)
Verapamil	Acute	37 (50)	30 (40)	27 (37)
	Routine	37 (53)	32 (46)	21 (30)
Beta-blocker	Acute	37 (50)	30 (41)	26 (35)
	Routine	33 (47)	30 (43)	22 (31)
Sotalol	Acute	0 (0)	0 (0)	3 (4)
	Routine	0 (0)	4 (5)	16 (23)†
Amiodarone	Acute	0 (0)	30 (40)	28 (38)
	Routine	0 (0)	6 (9)†	28 (40)

*Values expressed as n (%) of patients; †$p < 0.05$ acute versus routine group.

ECV1 = first-study electrical cardioversion; EoS = end of study; other abbreviations as in Table 1.

Table 3. Medication During the Study of Patients Randomized to the Digoxin Versus Verapamil

Drug	Strategy	At ECV1*	1 Month After ECV1*	Permanent AF/EoS*
Digoxin	Digoxin	70 (100)	68 (97)	54 (77)
	Verapamil	0 (0)†	4 (6)†	3 (4)†
Verapamil	Digoxin	0 (0)	0 (0)	1 (1)
	Verapamil	69 (93)†	63 (85)†	47 (64)†
Beta-blocker	Digoxin	42 (60)	34 (48)	24 (34)
	Verapamil	28 (38)†	32 (43)	24 (32)
Sotalol	Digoxin	0 (0)	2 (3)	12 (17)
	Verapamil	0 (0)	1 (1)	7 (10)
Amiodarone	Digoxin	0 (0)	18 (25)	31 (44)
	Verapamil	0 (0)	19 (25)	25 (34)

*Values expressed as n (%) of patients; †$p < 0.05$ digoxin versus verapamil group. Abbreviations as in Tables 1 and 2.

recurrences (15 vs. 21 patients in the acute vs. routine group, respectively; p = NS). Mean amiodarone dose and plasma levels of amiodarone and desethylamiodarone were not significantly different between successfully (1.3 ± 0.6 mg/l and 0.9 ± 0.3 mg/l, respectively) and unsuccessfully (1.4 ± 0.4 mg/dl and 0.8 ± 0.2 mg/dl) treated patients. Four patients refused further amiodarone therapy. Side effects of amiodarone led to discontinuation in 15% of patients (skin rash [n = 4], excessive prolongation of QT duration [n = 2], gastrointestinal problems [n = 2], thyreotoxicosis [n = 1], blurred vision [n = 1], and elevated liver enzymes > 3 times the upper level of normal [n = 1]). At the end of follow-up, 77% of patients (n = 111) still used phenprocoumon or acenocoumarol, 5% (n = 7) were on aspirin therapy, and 18% (n = 26) discontinued their anticoagulant therapy.

Efficacy of acutely repeated cardioversions. In the acute group, most re-ECVs were performed during the first week after the initial ECV (37 re-ECVs during the first week, and 12, 6, and 5 re-ECVs during the second, third, and fourth weeks after the initial ECV, respectively). Median time spent in SR between the first ECV and the first relapse was 3 (0 to 19) days; between the second ECV (re-ECV1) and the second relapse, 3 (0 to 119) days; and between re-ECV2 and the third relapse, 9 (1 to 478) days. Re-ECV1 in the acute group was performed <24 h in 94% of patients, re-ECV2 in 81% of patients <24 h, and re-ECV3 in 70% of patients. Thereafter, the number of patients with an acute re-ECV sharply decreased. Acute repeated ECVs were postponed predominantly because of unsuccessful ECVs necessitating amiodarone loading (Fig. 2). Progressive increase in duration of the repetitive episodes of SR were observed in 38% who underwent a second ECV (re-ECV1), in 38% undergoing a third ECV (re-ECV2), and in 14% undergoing a fourth ECV (re-ECV3). Atrial fibrillation was predominantly accepted because of failure of the strategy (71% vs. 95% in the acute vs. the routine group, respectively; p = NS). More refusals for a repeated ECV were observed in the acute group (29% vs. 5%, respectively; $p < 0.05$).

Verapamil versus digoxin. No significant differences in baseline characteristics were present (Table 1). To obtain adequate rate control, more patients in the digoxin group were treated with additional beta-blocker therapy (60% vs. 38%, respectively; p = 0.01) (Table 3). During 24-h Holter monitoring performed 2 weeks after inclusion mean heart rate was comparable in the verapamil versus the digoxin group: 82 ± 12 beats/min versus 84 ± 13 beats/min, respectively. Spontaneous conversion occurred in 12% (n = 9) of patients on verapamil versus 1% (n = 1) of patients on digoxin (p = 0.01). There was no significant difference in the time to the first relapse (Fig. 4). After 18 months of follow-up, AF was accepted in 28% (n = 21) (95% CI 19 to 40) versus 36% (n = 25) (95% CI 25 to 48) of the verapamil- versus the digoxin-treated patients, respectively (p = 0.33) (Fig. 5), despite more ECVs in the digoxin group (median of 3 vs. 2, $p < 0.001$, and ≥3 ECVs in 60% vs. 28% in the digoxin vs. verapamil group, respectively; $p < 0.001$). A total of 19 patients maintained SR after 1 ECV

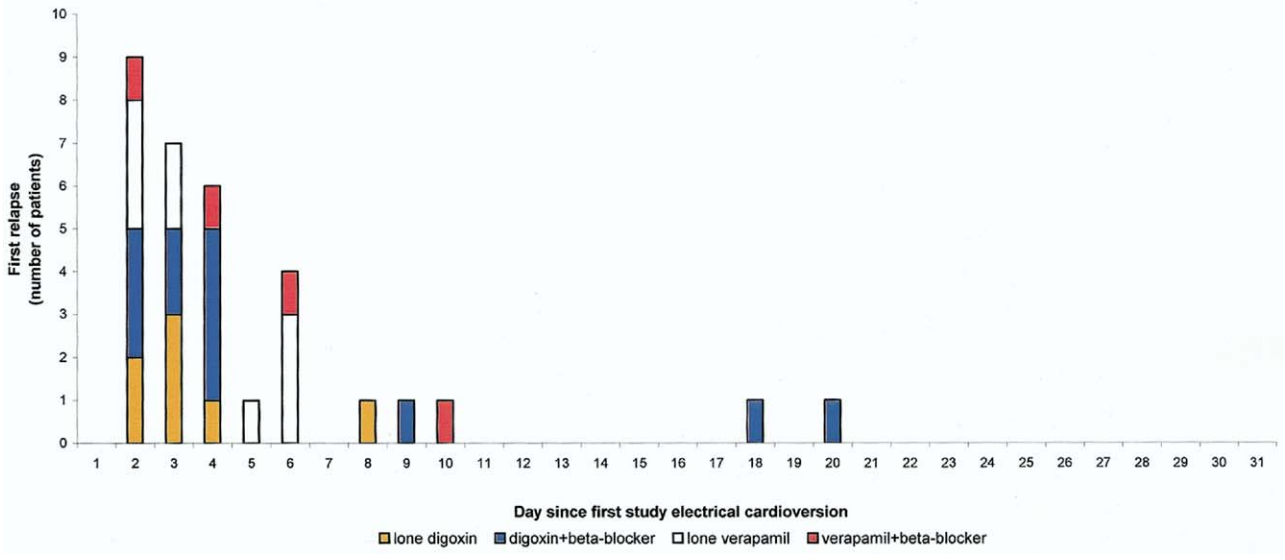

Figure 4. Time to first relapse in the acute group between digoxin- versus verapamil-treated patients.

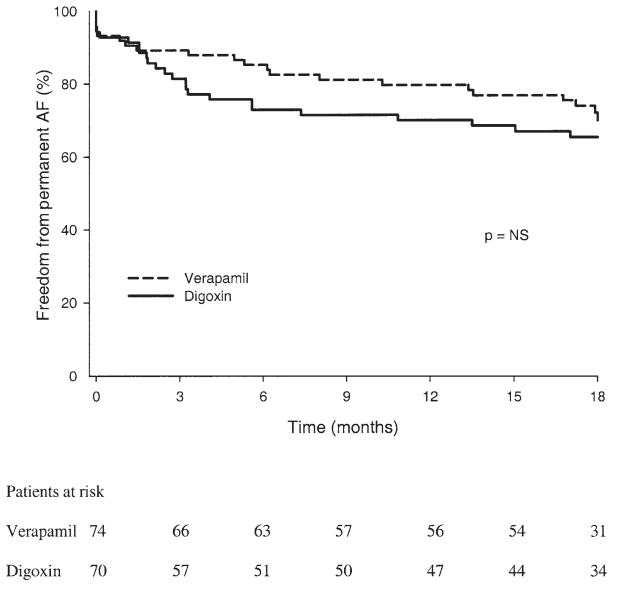

Figure 5. Freedom from permanent AF in digoxin- versus verapamil-treated patients. Abbreviations as in Figure 1.

(13 patients randomized to verapamil vs. 6 patients randomized to digoxin; p = NS). At the end of follow-up, 17% of patients in the digoxin group versus 10% in the verapamil group used sotalol, and 44% in the digoxin group versus 34% in the verapamil group were treated with amiodarone (both p = NS) (Table 3).

Thromboembolic complications and bleeding. Bleeding occurred in 6 patients (4%) during oral anticoagulant therapy (all patients had an INR >3.0). Two patients (1%) had a transient ischemic attack. There were no differences in anticoagulant therapy and complications between the groups.

Parameters related to occurrence of permanent AF. In the total patient group, multivariate analysis revealed that the use of digoxin monotherapy was the only parameter related to a higher occurrence of permanent AF (adjusted hazard ratio 2.2 [1.1 to 4.4], p = 0.02) (Table 4). From multivariate analysis, there was no evidence of interaction between ECV strategy (acute or routine) and drug strategy (verapamil or digoxin).

Outcome of cardioversions. First study ECV was performed in 129 patients. In 15 patients, no ECV was performed because of spontaneous conversion (n = 10), heart failure (n = 1, verapamil acute group), refusal (n = 2, verapamil routine group and digoxin routine group), stroke (n = 1, digoxin routine group), and respiratory insufficiency (n = 1, verapamil routine group) before the planned cardioversion. First study ECV was successful in 111 patients (86%) and unsuccessful in 8% because of shock failure and in 6% because of IRAF. No significant differences in this figure were observed between digoxin- and verapamil-randomized patients.

Quality of life. There were no significant differences in quality of life between the acute and the routine cardioversion groups. At the end of follow-up, scores on general health perception and bodily pain were significantly higher in the routine group compared to the acute group. At that time, the acute group showed a significant improvement on 3 subscales (physical role limitations, social functioning, and vitality), whereas patients randomized to the routine group demonstrated a significant improvement on 6 subscales. No significant differences between verapamil- and digoxin-randomized patients were observed at baseline or at 18 months of follow-up. At the end of follow-up, the digoxin group showed a significant improvement on 5 subscales, and the verapamil group on 3 subscales (data not shown). In patients who were in SR at 18 months, quality of life was not significantly different compared to patients in AF.

DISCUSSION

This study shows that an acute serial cardioversion strategy does not improve the outcome of rhythm-control therapy. Also, in a serial cardioversion strategy, verapamil does not have beneficial effects. Finally, digoxin monotherapy should not be instituted in patients in whom rhythm control is indicated.

Acute serial cardioversion. This study does not show any advantage of an acute serial cardioversion strategy. Theoretically, an acute cardioversion strategy may, by enhancing and consolidating reversed remodeling, improve arrhythmia outcome in persistent AF managed with serial cardioversions (9–12). Similar to us, Fynn et al. (13) designed an early repeated internal ECV strategy to support recovery from electrical remodeling and to reduce subsequent AF recurrences. Although they could demonstrate reversal of electrical remodeling, no beneficial effect on maintenance of SR was observed, comparable to our findings. Several explanations may be responsible. First, time to repeated

Table 4. Predictors of Occurrence of Permanent AF

	Univariate Model			Multivariate Model		
	HR	95% CI	p	HR	95% CI	p
Lone digoxin use	2.4	1.2–4.7	0.013	2.2	1.1–4.4	0.02
Diastolic BP >86 mm Hg	1.9	1.0–3.6	0.06	1.9	1.0–3.7	0.054
ACE inhibitor or ARB use	0.5	0.3–1.0	0.06			
Total AF duration (yrs)	1.1	1.0–1.1	0.07			

No interaction term was found statistically significant.
BP = blood pressure; CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

cardioversion may have been too long. Even though repeated cardioversions were performed within 24 h in the majority of the patients in both studies after the first and second re-ECV, that may not have been early enough to succeed with such a strategy. The delay, in part, was caused by the occurrence of shock failure and/or IRAF, necessitating amiodarone loading, and by the patient's (ultimate) refusal of repeated ECV. Second, the time in SR after the first, second, and third cardioversion may not have been enough to overcome remodeling. In line with this, Tieleman et al. (12) showed that flecainide may recover its antiarrhythmic conversion efficacy after cardioversion of AF, but only if AF relapses last <10 h after SR has lasted for more than 4 days. Third, other factor(s), e.g., structural remodeling, may be present that require a stronger antiarrhythmic effect to overcome relapses of AF, if reversible at all (18,19). Recent experimental data further substantiated the importance of factor(s) other than electrical remodeling alone for the persistence of AF. Todd et al. (20) demonstrated that sequential 4-week periods of maintained AF with 2 days of SR in between, increased AF stability and inducibility independent of the baseline atrial effective refractory period. The latter suggests that despite acute cardioversions, consecutive episodes of AF cumulatively may increase the degree of remodeling, prohibiting complete reversal of (structural) remodeling.

Calcium-channel blockade for prevention of AF. Experimentally, prevention of calcium overload by calcium antagonists may decrease intractability of AF by preventing remodeling processes (21). Although effective if prescribed in combination with antiarrhythmic drugs (22–24), verapamil monotherapy seems ineffective to prevent subacute recurrences (25,26). The discrepancy with experimental data may relate to the fact that in patients, calcium-lowering treatment is almost always started after the start of AF (27). In a serial cardioversion strategy, remodeling may happen again and again, and in this setting verapamil has not been tested before. Unfortunately, this strategy also did not demonstrate a beneficial effect of verapamil, and also not for the occurrence of IRAF, as has previously been described (28). There are several explanations for this disappointing result. First, in order to obtain adequate rate control, in 60% of the patients randomized to digoxin, a beta-blocker was added. Beta-blockers also lower intracellular calcium and may thus have ameliorated outcome in the digoxin arm. On the other hand, Bertaglia et al. (29) observed that pretreatment with verapamil and amiodarone prevented electrical remodeling, whereas the combination of metoprolol and amiodarone only accelerated recovery of electrical remodeling. Second, as discussed in the preceding text, consecutive episodes of AF cumulatively increase the degree of remodeling, prohibiting prevention of remodeling by calcium-lowering therapy (20). The previously described profibrillatory effects of verapamil (30), however, were not observed. Multivariate analysis showed that patients treated with digoxin as monotherapy more frequently relapsed into permanent AF.

Quality of life. Quality of life is significantly reduced in patients with AF and is not importantly affected by a rate- or rhythm-control strategy (1,16). In this study, in all randomized groups, several subscales of the SF-36 improved during follow-up whether or not SR was maintained. Thus, both adequate rate control and successful rhythm control induced a comparable improvement in quality of life. This improvement may be explained, at least in part, by the fact that at baseline, 4 weeks ahead of the first-study ECV, quality of life was assessed before adequate rate control was obtained. This also may clarify why we did not observe any beneficial effect of SR. Two SF-36 domains were significantly higher in the routine compared to the acute ECV-randomized patients. During follow-up, however, improvement occurred on 6 subscales in the routine group versus 3 in the acute group. This may be a sign that an acute ECV strategy impairs quality of life.

Study limitations. This is a relatively small study. A replication of our study, possibly in the setting of non-inferiority, would be of help in establishing an optimal rhythm-control strategy. Furthermore, the acute serial cardioversion strategy, including acutely repeated cardioversion within 24 h, could not always be accomplished, either because of shock failure or IRAF, or patient refusal. This, however, is an important finding indicating that an acute serial cardioversion strategy is not feasible in clinical practice. The routine arm, like the acute arm, might have benefited from the temporary use of amiodarone to suppress subacute recurrences, to the effect that maybe the routine arm would have shown even better results than the acute arm. However, we felt not justified to use amiodarone in the routine arm because it was not part of the clinical routine at the time of the study, and we wanted to avoid the adverse effects of chronic amiodarone as much as possible. Finally, the verapamil hypothesis also could not be tested thoroughly because, for clinical reasons, beta-blockers had to be instituted as an additional rate-control drug in the digoxin-randomized patients. Beta-blockers also have calcium-lowering capacities.

Conclusions. An acute serial cardioversion strategy does not improve rhythm control. Furthermore, verapamil has no beneficial effect in a serial cardioversion strategy. Therefore, the role of calcium-lowering drugs in preventing AF-induced electrical remodeling in clinical practice, which in the recent past has been much emphasized, is at least arguable.

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REFERENCES

1. Wyse DG, Waldo AL, DiMarco JP, et al., Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825–33.
2. Van Gelder IC, Hagens VE, Bosker HA, et al., Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002; 347:1834–40.
3. Singh BN, Singh SN, Reda DJ, et al. Amiodarone versus sotalol for atrial fibrillation. N Engl J Med 2005;352:1861–72.
4. Pappone C, Rosanio S, Augello G, et al. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. J Am Coll Cardiol 2003;42:185–97.
5. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation 1995;92:1954–68.
6. Gaspo R, Bosch RF, Talajic M, Nattel S. Functional mechanisms underlying tachycardia-induced sustained atrial fibrillation in a chronic dog model. Circulation 1997;96:4027–35.
7. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res 2002;54:230–46.
8. Manning WJ, Silverman DI, Katz SE, et al. Impaired left atrial mechanical function after cardioversion: relation to the duration of atrial fibrillation. J Am Coll Cardiol 1994;23:1535–40.
9. Tieleman RG, Van Gelder IC, Crijns HJ, et al. Early recurrences of atrial fibrillation after electrical cardioversion: a result of fibrillation-induced electrical remodeling of the atria? J Am Coll Cardiol 1998; 31:167–73.
10. Yu WC, Lee SH, Tai CT, et al. Reversal of atrial electrical remodeling following cardioversion of long-standing atrial fibrillation in man. Cardiovasc Res 1999;42:470–6.
11. Hobbs WJ, Fynn S, Todd DM, Wolfson P, Galloway M, Garratt CJ. Reversal of atrial electrical remodeling after cardioversion of persistent atrial fibrillation in humans. Circulation 2000;101:1145–51.
12. Tieleman RG, Van Gelder IC, Bosker HA, et al. Does flecainide regain its antiarrhythmic activity after electrical cardioversion of persistent atrial fibrillation? Heart Rhythm 2005;2:223–30.
13. Fynn SP, Todd DM, Hobbs WJ, Armstrong KL, Fitzpatrick AP, Garratt CJ. Clinical evaluation of a policy of early repeated internal cardioversion for recurrence of atrial fibrillation. J Cardiovasc Electrophysiol 2002;13:135–41.
14. Schotten U, Duytschaever M, Ausma J, Eijsbouts S, Neuberger HR, Allessie M. Electrical and contractile remodeling during the first days of atrial fibrillation go hand in hand. Circulation 2003;107:1433–9.
15. Fuster V, Ryden LE, Asinger RW, et al., American College of Cardiology/American Heart Association Task Force on Practice Guidelines; European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation); North American Society of Pacing and Electrophysiology. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary—a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation), developed in collaboration with the North American Society of Pacing and Electrophysiology. Circulation 2001;104:2118–50.
16. Hagens VE, Ranchor AV, Van Sonderen E, et al., RACE Study Group. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the Rate Control Versus Electrical Cardioversion (RACE) study. J Am Coll Cardiol 2004;43:241–7.
17. Van Gelder IC, Crijns HJ, Tieleman RG, et al. Chronic atrial fibrillation. Success of serial cardioversion therapy and safety of oral anticoagulation. Arch Intern Med 1996;156:2585–92.
18. Everett TH 4th, Li H, Mangrum JM, et al. Electrical, morphological, and ultrastructural remodeling and reverse remodeling in a canine model of chronic atrial fibrillation. Circulation 2000;102:1454–60.
19. Ausma J, Van der Velden HM, Lenders MH, et al. Reverse structural and gap-junctional remodeling after prolonged atrial fibrillation in the goat. Circulation 2003;107:2051–8.
20. Todd DM, Fynn SP, Walden AP, Hobbs WJ, Arya S, Garratt CJ. Repetitive 4-week periods of atrial electrical remodeling promote stability of atrial fibrillation: time course of a second factor involved in the self-perpetuation of atrial fibrillation. Circulation 2004;109: 1434–9.
21. Tieleman RG, De Langen C, Van Gelder IC, et al. Verapamil reduces tachycardia-induced electrical remodeling of the atria. Circulation 1997;95:1945–53.
22. De Simone A, Stabile G, Vitale DF, et al. Pretreatment with verapamil in patients with persistent or chronic atrial fibrillation who underwent electrical cardioversion. J Am Coll Cardiol 1999;34:810–4.
23. De Simone A, De Pasquale M, De Matteis C, et al. VErapamil plus antiarrhythmic drugs reduce atrial fibrillation recurrences after an electrical cardioversion (VEPARAF study). Eur Heart J 2003;24: 1425–9.
24. Fetsch T, Bauer P, Engberding R, et al., Prevention of Atrial Fibrillation after Cardioversion Investigators. Prevention of atrial fibrillation after cardioversion: results of the PAFAC trial. Eur Heart J 2004;25:1385–94.
25. Van Noord T, Van Gelder IC, Tieleman RG, et al. VERDICT: the Verapamil versus Digoxin Cardioversion Trial: A randomized study on the role of calcium lowering for maintenance of sinus rhythm after cardioversion of persistent atrial fibrillation. J Cardiovasc Electrophysiol 2001;12:766–9.
26. Lindholm CJ, Fredholm O, Moller SJ, et al. Sinus rhythm maintenance following DC cardioversion of atrial fibrillation is not improved by temporary precardioversion treatment with oral verapamil. Heart 2004;90:534–8.
27. Kurita Y, Mitamura H, Shiroshita-Takeshita A, et al. Daily oral verapamil before but not after rapid atrial excitation prevents electrical remodeling. Cardiovasc Res 2002;54:447–55.
28. Daoud EG, Hummel JD, Augostini R, Williams S, Kalbfleisch SJ. Effect of verapamil on immediate recurrence of atrial fibrillation. J Cardiovasc Electrophysiol 2000;11:1231–7.
29. Bertaglia E, D'Este D, Zerbo F, Michieletto M, Pascotto P. Effects of verapamil and metoprolol on recovery from atrial electrical remodeling after cardioversion of long-lasting atrial fibrillation. Int J Cardiol 2003;87:167–72.
30. Duytschaever MF, Garratt CJ, Allessie MA. Profibrillatory effects of verapamil but not of digoxin in the goat model of atrial fibrillation. J Cardiovasc Electrophysiol 2000;11:1375–85.

APPENDIX

The following persons participated in the Verapamil vERsus Digoxin Cardioversion Trial: University Medical Center Groningen; I. C. Van Gelder, M. E .W. Hemels, T. Van Noord; University Hospital Maastricht, H. J. G. M. Crijns, R. G. Tieleman; Rijnstate Hospital, Arnhem; H. A. Bosker; Academic Medical Center, Amsterdam; A. A. M. Wilde, N. Colman; Isala Klinieken Zwolle, J. C. A. Hoorntje; Martini Ziekenhuis, Groningen, J. L. Posma; Stichting Deventer Ziekenhuizen, Deventer; D. J. A. Lok.